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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/619,799	07/14/2003	Glenn H. McGall	2719.2012-004	7882
42145	7590	08/17/2006	EXAMINER	
FISH & NEAVE IP GROUP ROPES & GRAY ONE INTERNATIONAL PLACE BOSTON, MA 02110			SHIBUYA, MARK LANCE	
			ART UNIT	PAPER NUMBER
			1639	

DATE MAILED: 08/17/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)	
	10/619,799	MCGALL ET AL.	
	Examiner	Art Unit	
	Mark L. Shibuya	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 05 July 2006.
- 2a) ☒ This action is **FINAL**.                      2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 10 and 23-34 is/are pending in the application.
- 4a) Of the above claim(s) 10 and 30 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 23-29 and 31-34 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |   |   |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)                        | 4) <input type="checkbox"/> Interview Summary (PTO-413)                     |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)    | Paper No(s)/Mail Date. _____  |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____   | 6) <input type="checkbox"/> Other: _____                                    |

### **DETAILED ACTION**

1. Claims 10, 23-34 are pending. Claims 10 and 30 are withdrawn. Claims 23-29 and 31-34 are examined.

#### ***Election/Restrictions***

2. Claims 10 and 30 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 7/22/2005.

#### ***Priority***

3. This application, filed 7/14/2003, states that it is a divisional of 09/102,986, filed 6/22/1998, now abandoned.

#### ***Information Disclosure Statement***

4. Applicant argues that WO 93/04145, which corresponds to cite no. AP, in the IDS, entered 10/17/2003, has an English abstract. This is persuasive, and cite no. AP has been initialed on said IDS. The document has been considered only to the extent of the English abstract. The IDS is attached to the instant Office action; duplicative citations are crossed off.

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5. The citations of references AZ2 and AR3 as cited in the Information Disclosure Statement (IDS), entered 10/17/2003, are not provided dates of publication and so are lined-out on the IDS; however references AZ2 and AR3 are considered. See, previous Office action, mailed 11/30/2005, at p. 3.

Applicant argues that in parent Application No. 09/102,986, no publication dates for the citations in question, were provided on the Form PTO-892, and therefore, no publication dates should be required on the Form 1449, entered in the instant application.

Applicant's argument has been considered but is not persuasive. 37 CFR 1.98(b)(5) states: "Each publication listed in an information disclosure statement must be identified by publisher, author (if any), title, relevant pages of the publication, date, and place of publication."

Thus the rules regarding IDS clearly require dates in the citations for publications referenced in IDS. The examiner respectfully submits that any incompleteness of the Form 892 in abandoned parent Application No. 09/102,986, is not sufficient reason to allow the instant examiner to excuse non-compliance with the IDS rules in the instant application. As stated in the previous Office action, references AZ2 and AR3 have been considered, although the citation to the said references continue to be lined through on the listing of the IDS, entered 10/17/2003.

***Withdrawn Claim Rejections***

6. The rejection of Claims 28, 29, 32 and 33 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is withdrawn in view of applicant's amendments to the claims.

***Claim Rejections - 35 USC § 112, First Paragraph***

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claims 23-29 and 31-34 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is for new matter. This rejection is necessitated by applicant's amendments to the claims.

Applicant has amended withdrawn claim 10, and claims 23 and 32, to state the language "the same surface of a support" (twice in claim 23) or "the same surface of said modified support", (as in claim 32). Applicant argues that support for the amendment may be found, for example, at p. 7, lines 8-15.

The examiner respectfully submits that the specification as filed, does not provide support for applicant's amendments to the claims. For example, at the portion of the specification cited by applicant for support, the specification states:

Substrate: A material having a rigid or semi-rigid surface. In many embodiments, at least one surface of the substrate will be substantially flat, although in some embodiments it may be desirable to physically separate synthesis regions for different polymers with, for example, wells, raised regions, etched trenches, or the like. In some embodiments, the substrate itself contains wells, trenches, flow through regions, etc. which form all or part of the synthesis regions. According to other embodiments, small beads may be provided on the surface, and compounds synthesized thereon may be released upon completion of the synthesis.

Specification at p. 7, lines 8-15. The examiner respectfully submits that this passage does not provide support for the limitation of synthesizing an array on a "same surface of a support". One thing there is no mention, explicit or otherwise, of the concept of a "same surface" of a support in the above quotation.

Applicant must point, with particularity, as to where in the specification as filed, specific support may be found for the new claim limitation introduced by amendment.

***Claim Rejections - 35 USC § 112, Second Paragraph***

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 23-29 and 31-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter

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which applicant regards as the invention. This rejection is necessitated by applicant's amendments to the claims.

Claim 23 and 32 state the language "the same surface of a support" (twice in claim 23) or "the same surface of said modified support", (as in claim 32), which renders the claims vague and indefinite. The limitation " same surface of a support " is not defined by the claims, the specification does not provide a standard for ascertaining when surfaces of a support are the same or different, and one of skill in the art would not be reasonably apprised of the metes and bound of the claimed invention. For example, wells in a single 96 well plate might be said to be on the same surface of the support, or on different surfaces, even though those surface or continuous or contiguous. Because the specification does not provide a limiting definition for same surfaces of a support and because the claims omit the essential structural cooperative relationships of the surfaces on the support, such omission amounting to a gap between the necessary structural connections, the examiner respectfully submits that the claims are vague and indefinite.

***Claim Rejections - 35 USC § 103***

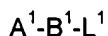
11. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

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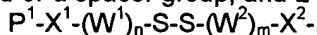
12. Claims 23-29 and 31-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over any of **Kumar et al.**, Tetrahedron Letters, 32 (7): 967-970, 1991 (IDS entered 10/17/2003, reference no. AS3), **Salo et al.**, Collect. Czech. Chem. Commun., 1996, 61 (Spec. Issue), S110-S111, referred to as **Salo 1**, IDS entered 10/17/2003, reference no. AT3) or **Salo et al.**, Bioconjugate Chem. 1998, Vol. 9, No. 3, pp. 365-371, (referred to as **Salo 2**, IDS entered 10/17/2003, reference no. AU3), each taken separately, and **Lockhart et al.**, US 5,556,752.

This rejection is maintained for the reasons of record as set forth in the previous Office action. The rejection is copied below for the convenience of the reader.

The claims are drawn to methods of synthesizing an array of diverse polymers on a substrate, comprising: (a) providing a modified substrate for use in solid phase chemical synthesis, said substrate having the formula:



wherein A is a solid support, B is a bond or a spacer group, and L is a linking group having the formula:



wherein,  $P^1$  is a protecting group;  $X^1$  and  $X^2$  are each independently selected from the group consisting of a bond, -O-, -NH-, -NR- and -CO2-, wherein R is a lower alkyl group having one to four carbon atoms;  $W^1$  and  $W^2$  are each independently selected from the group consisting of methylene, oxyethylene and oxypropylene; and n and m are each independently integers of from 2 to 12 with the proviso that n and m are not the same when  $W^1$  and  $W^2$  are the same; and (b) preparing an array of diverse polymers on said modified substrate; and variations thereof.

**Kumar et al.**, Tetrahedron Letters, 32 (7): 967-970, 1991 (IDS entered 10/17/2003, reference no. AS3), throughout the publication, disclose a "solid phase method for the synthesis of oligonucleotide-3'-phosphates (see especially Title, Abstract). **Kumar et al.** synthesize a "universal Controlled-Pore Glass (CPG)-based support compatible with established phosphoramidite approach of DNA synthesis", (see page 967). This solid support is unsymmetrical and particularly reads on those claimed (see Scheme 1, compound 6). Note that although the linkage between the solid support and the first sulfur of the disulfide is not species shown in the Scheme, when one looks to the text for the synthesis of this solid support (synthesis of compound 1 from Scheme 1) it is shown that the linkage between the first sulfur of the disulfide and the CPG is accomplished with 3-mercaptopropyltrimethoxysilane (see p. 967, last paragraph and footnote 8 of the reference). Thus the linker of **Kumar et al.**, reads on the instant claims where  $B^1$ =a bond,  $X^1=X^2=O$  and  $W^1=W^2$ =methylene, with n=2 (see compound 6 in Scheme 1) and m=3 (from the mercaptopropyl group). **Kumar et al.**, at p. 968, teach cleavage of the disulfide linkage to the support. Moreover, **Kumar et al.** disclose that "the disulfide linkage containing polymer support 6 was stable to the coupling, deprotection, capping and oxidative conditions used in the solid phase phosphoramidite chemistry", (p. 968)). The protecting group ( $P^1$ ) DMT is also disclosed in **Kumar et al.** (see Scheme 1).

**Salo 1**, throughout the publication, discloses asymmetrical disulfide tethered solid supports for oligonucleotide synthesis. See particularly Scheme 1 of **Salo 1**. The linkers allow for the synthesis of oligonucleotide-3'-phosphates (see, for example, first paragraph) and were tested for their stability. The reference discloses that a chain longer than 2 carbons is needed between the spacer groups and the first



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sulfur of the disulfide to avoid instability (see p. S111, last paragraph). The reference discloses solid supports where  $P^1$ =DMT,  $B^1$ =a spacer,  $X^1$ =O,  $X^2$ =a bond and  $W^1=W^2$ =methylene, with n and m being unequal. Specifically, see compounds 4-11 in Scheme 1 of the reference. Salo 1, at p. S111, teaches the release of oligonucleotides from TentaGel by cleavage of the disulfide linker.

**Salo 2**, throughout the publication, teaches asymmetrical disulfide tethered solid supports for oligonucleotide synthesis. The reference discloses a general scheme for labeling oligonucleotides on a solid support (see Scheme 1) and discloses specific linkers to carry out this process. See particularly Scheme 2 and Table 1 of Salo 2. The linkers allow for the synthesis of oligonucleotide-3'-phosphates (see, for example, Abstract) and were tested for their stability. The reference discloses that a chain longer than 2 carbons is needed between the spacer group and the first sulfur of the disulfide to avoid instability (see Abstract). The reference discloses solid supports where  $P^1$ =DMT,  $B^1$ =a spacer,  $(C(O)NH)$ ,  $X^1$ =O,  $X^2$ =a bond and  $W^1=W^2$ =methylene, with n and m being unequal. Specifically, see supports S2a-S5b in Table 1 of the reference. Salo 2 at p. 365, notes the use of disulfide based tethers in automated oligonucleotide synthesis and teaches that such tethers withstand basic conditions rather well, and that they readily undergo reductive cleavage.

None of Kumar et al., Salo1 or Salo 2, each taken separately, disclose an array of diverse polymers on a substrate, as in claims 23 and 32, or photolabile protecting groups, as in claims 24-26 and 33.

**Lockhart et al.**, US 5,556,752, throughout the patent, and at col. 14, line 47-col. 15, line 18, teach arrays of oligonucleotides, including those prepared by pin based synthesis, wherein a substrate may be provided with a spacer having active sites, and wherein the active sites may be protection optionally with protecting groups, such as Fmoc, BOC, and wherein the spacer may provide for a cleavable function by way of, for example, exposure to acid or base, reading on releasing polymers from the substrate, as in claim 34. Lockhart et al., at, for example, col. 11, 51-67, teach synthesizing libraries on a solid support having a plurality of preselected regions. Lockhart et al., at col. 12, line 1 to col. 13, line 24, teach the use of spacers modified with photolabile groups for light-directed synthesis of polymer arrays on solid supports using, e.g., the VLSIPS method, wherein deoxynucleoside monomers are coupled to produce libraries, as in claim 32 and 33.

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to have used methods comprising a modified substrate having a linker of the formula  $P^1-X^1-(W^1)_n-S-S-(W^2)_m-X^2$ , as taught by any one of Kumar et al., Salo 1 or Salo 2, each taken individually, and wherein an array of diverse polymers are synthesized onto the linkers, and wherein  $P^1$  is a photolabile protecting group on the linker that is used in coupling monomers of polymers, as taught by Lockhart et al.

One of ordinary skill in the art would have been motivated to use methods for synthesizing arrays on a modified substrate comprising a linker the formula  $P^1-X^1-(W^1)_n-S-S-(W^2)_m-X^2$ , because each of Kumar et al., Salo 1 and Salo 2, teach their use in making oligonucleotide polymers on surfaces by linking the polymer building blocks to substrates, and cleavage of such disulfide-containing linkers to release the polymers, and because Lockhart et al. teach cleavage of linkers binding oligonucleotides libraries to substrates, and wherein the oligonucleotides are diverse members of large scale chemical arrays. One of ordinary skill in the art would have been motivated to use linkers having protecting groups that are photolabile, in order to create polymers using light-directed methods of polymer synthesis on solid substrates, as taught by Lockhart et al.

One of ordinary skill in the art would have had a reasonable expectation of success in making and using arrays of polymers on modified substrates comprising linker of the formula  $P^1-X^1-(W^1)_n-S-S-(W^2)_m-X^2$ , because Kumar et al., Salo 1 and Salo 2, teach the use of such linkers and because the production of arrays of polymers on solid substrates using linkers, including linkers with photolabile protecting groups, was well known in the art at the time the invention was made.

### Response to Arguments

Applicant argues that the cited prior art references do not disclose all elements of the claimed invention. Applicant argues that independent claims 10 and 23 have been amended to recite that an array of diverse small ligand molecules or polymers is prepared on the same surface of a support (as opposed to physically separated surfaces, see p. 7, lines 8-15 of the specification). Applicant states:

Lockhart teaches the use of cleavable linker groups only in conjunction with pin-based synthetic methods (see column 15, lines 15-17). Lockhart has no other teaching or suggestion regarding cleavable linker groups. Pin-based synthetic methods use a support where only one polymer species is produced per surface, in contrast to the instantly claimed method. An illustration of a substrate suitable for pin-based methods is shown in Fig. 1 of U.S. Patent No. 5,288,514, which was incorporated by reference by Lockhart (copy attached hereto as "Exhibit A"). While a support as a whole may include more than one polymer species, the different species are located on different pins, and, by extension, different surfaces. Thus, Lockhart does not teach or otherwise suggest preparing an array of diverse small ligand molecules or polymers, where the diverse polymers are located together on the same surface of a substrate. Thus, even in conjunction with cleavable linker groups, such as those taught by Kumar, Salo 1 and Salo 2, the art of record does not teach every element of the claimed method as amended.

Reply at pp. 6-7, bridging paragraph.

Applicant's arguments, entered 6/2/2006, have been fully considered but they are not persuasive.

The examiner respectfully submits that applicant's amendments to the claims introducing the new limitation synthesizing an array on the "same surface of a support", fails to overcome the instant rejection.

Firstly, claims must be given their broadest reasonable interpretation consistent with the supporting description. In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). See, e.g., *Invitrogen Corp v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368, 66 USPQ2d 1631, 1634 (Fed. Cir. 1997); and MPEP 211.03. The "same surface of a support" may be interpreted as all continuous or contiguous areas on a support. Thus, in applicant's Exhibit, the pins, which are contiguous and continuous, have the same surface upon which an array may be constructed.

The arguments of counsel cannot take the place of evidence in the record. *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a *prima facie* case of obviousness."). MPEP 2145. Applicant, in the Reply at p. 7, states: "Pin-based synthetic methods use a support where only one polymer species is produced per surface, in contrast to the instantly claimed method." The examiner respectfully submits that this is mere argument of counsel. The examiner respectfully requests that applicant fails to provide objective evidence for this conclusion regarding ultimate fact, as the examiner does not find applicant's interpretation of Exhibit A to be persuasive.

Furthermore, the prior art reference of Lockhart et al., at col. 12-14, in exemplifying the manufacture of libraries on a single substrate, (which reasonably would read on the "same surface of a support"), states at col. 12, lines 28-33, that pin based methods are also contemplated in said manufacture. Lockhart, at col. 12, lines 35-36,

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contemplates the use of spacers, (which encompasses linkers), on the surfaces of a solid support. As applicant notes, Lockhart teaches the use of cleavable linker groups in conjunction with pin-based synthetic methods. As stated in the previous Office action, such a disclosure may be found in Lockhart at, e.g., col. 14, line 48-col. 15, line 18. Once again, examiner respectfully notes that Lockhart, at col. 15, lines 15-18, teaches that "the spacer may provide for a cleavable function by way of, for example, exposure to acid or base." Therefore, the examiner respectfully submits that the aforementioned prior art reference continue to render the claims obvious, even after amendment.

### ***Conclusion***

13. Claims 23-29 and 31-34 stand finally rejected.

14. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the

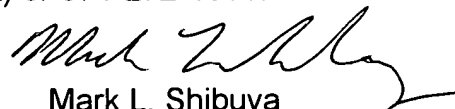
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shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Shibuya whose telephone number is (571) 272-0806. The examiner can normally be reached on M-F, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



Mark L. Shibuya  
Examiner  
Art Unit 1639